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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,245	07/22/2003	Shuichi Mizuno	3831.08	9296

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EXAMINER	
NAFF, DAVID M	
ART UNIT	PAPER NUMBER
1657	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/625,245	MIZUNO ET AL	
	Examiner	Art Unit	
	David M. Naff	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance.. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment of 11/13/06 in response to an office action of 8/8/06 canceled claims 21-42, and added new claims 43-62.

Claims examined on the merits are 43-62, which are all claims in the application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 43-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims define the construct in terms of process steps that make the claims product-by-process. The claims are confusing and unclear by not setting forth clear, distinct and positive process steps in the order in which they are carried out such that it is clear as to the functional relationship of each step to all other steps, and how the steps function to produce the construct. Since the claims are reciting process steps, the correct product-by-process form should be used, and the claims should require the construct to be prepared by a "process comprising", and then positively recite steps of the process in the order they are performed. Reciting process steps and conditions after "wherein" does not recite positive steps. Reciting "wherein" should be used only when defining components of the construct, and not when reciting process steps. See claim 1 of patent

6,949,252 that issued from parent application 10/104,677 as how to positively recite process steps, and properly use "wherein".

Claim 43 is unclear after which step the immature hyaline cartilage construct is obtained. If the immature hyaline cartilage has the ratio in the last line of claim 43, this should be made clear. Furthermore, if the ratio of immature hyaline cartilage is lower than 95:5 (last line of claim 43) and the ratio of mature hyaline cartilage is 95:5, immature hyaline cartilage having a ratio only slightly lower than 95:5 will be essentially the same as mature hyaline cartilage, and indistinguishable therefrom.

In line 1 of claim 43, "immature hyaline cartilage" and "neo-cartilage", and where recited in any other claims, are uncertain as to meaning and scope. Being "immature" and "neo" is relative and subjective, and it would be uncertain as to cartilage that is immature and neo and not immature and neo.

Reciting "(neo-cartilage)" in line 1 of claim 43 is unclear as to how this limitation further limits the cartilage construct.

In the last line of claim 43, reciting "%" after the ratio "95:5" is confusing since a ratio is not normally recited as a percent, and the specification (page 22, line 7) does not recite the ratio as a percent.

In line 4, claim 43 is unclear as to conditions that constitute a treatment regimen that activates. Without knowing the treatment regiment, one cannot know when the chondrocytes are activated as in lines 5-9. If the treatment regiment is the perfusion in lines 25-31,

the regiment and activating should be deleted from the claim preamble and recited as positive process steps when carried out. Reciting steps broadly in the claim preamble and then more specifically later in the claim confuses the process.

In lines 10-12, claim 43 is unclear as to where and when chondrocytes are previously inactive.

In lines 27-29, claim 43 is unclear by requiring a constant hydrostatic pressure having a frequency. How can a constant pressure have a frequency? This also applies to claim 56.

Bridging lines 32 and 33 of claim 43, there is not clear antecedent basis for "the newly synthesized extracellular matrix".

In the last line of claim 43, reciting "the neo-cartilage construct" does not have clear antecedent basis since line 1 of the claim requires an immature hyaline cartilage construct.

Claim 48 is unclear as to when in claim 43 the chondrocytes are in a gel as required. How does the gel relate to the support matrix in claim 43? Is the gel the matrix?

Claim 49 is unclear how a collagen gel can be a collagen solution.

In line 2 of claim 51, "sol-gel" is not a material that can be a matrix. Sol-gel defines a process and not a material. It is suggested the claim recite "gelled sol".

Claim 52 is unclear how fibronectin, laminin, bioactive peptide, growth factor, cytokine form the matrix. These are not materials that normally form a matrix. In the last line of the claim, "a copolymer

thereof" is unclear as to materials referred to as being a copolymer. Is copolymer thereof referring to all previous materials recited? Furthermore, all of the materials recited before "copolymer thereof" are not materials that normally form a copolymer, and how the materials form a copolymer is unclear.

In claims 57 and 58, there is not clear antecedent basis for "the metabolic activation".

In claims 59 and 60, there is not clear antecedent basis for "the support matrix construct".

Claim 61 is unclear as to whether the medium is the perfusion medium of claim 43 or some other medium. It is suggested the claim be amended in line 2 by changing "a medium" to --- said perfusion medium ---, and changing "a medium perfusion" to --- perfusion medium ---.

In the last line of claim 61, "insulin-transferring-sodium selenite" is uncertain as to how insulin-transferring defines sodium selenite. Insulin is not required in the process of claim 61, and insulin transfer cannot occur. Furthermore, sodium selenite is the same compound irrespective of whether insulin transfer occurs, and "insulin-transferring" does not limit the composition of sodium selenite. It is suggested "insulin-transferring" be deleted.

Claim Rejections - 35 USC § 102

Claims 43-47 and 44-62 are rejected under 35 U.S.C. 102(a) as being anticipated by Smith et al (6,528,052 B1).

The claims are drawn to an immature hyaline cartilage construct for implantation into a cartilage lesion. The construct is prepared

by isolating inactive chondrocytes by subjecting cartilage to enzymatic digestion, expanding the chondrocytes in a medium containing serum, suspending the expanded chondrocytes in a solution and seeding in a support matrix, and activating the seeded chondrocytes by perfusion with a medium at a flow rate of 1-500 μL per minute under cyclic or constant hydrostatic pressure of 0.01-10 MPa above atmospheric pressure at a frequency of 0.01-1 Hz for 1 hour to 30 days followed by a resting period from 1-60 days, and wherein following the regiment, a ratio of newly synthesized extracellular matrix to a number of chondrocytes in the construct is lower than 95:5.

Smith et al disclose repair and regeneration of cartilage by a process that involves *in vivo*, *ex vivo* or *in vitro* treatment of cartilage or cartilage cells (chondrocytes) in a scaffold or support by using a loading regiment involving conditions of intermittent application of periods of hydrostatic pressure followed by periods of recovery *in situ* (col 4, lines 25-31, and col 7, line 30 to col 8, line 8). The recovery period can be at atmospheric or low constant pressure (col 7, lines 48-50). *In* vitro treatment is performed by obtaining cartilage cells from cartilage, and applying the loading regiment conditions while culturing the cartilage cells in suspension within a scaffold/support, and implanting the resultant tissue or cells into a patient (col 9, lines 23-30, and col 11, lines 5-9). Articular chondrocytes (col 16, line 65) are isolated from cartilage using enzyme digestion (col 17, line 4). The chondrocytes can be

autologous or not autologous (col 9, line 33). Articular cartilage can be regenerated and repaired (col 1, lines 41-43).

Smith et al disclose process conditions essentially the same as process conditions required by the present claims, and the process of Smith et al inherently produces an immature hyaline cartilage construct having a ratio of synthesized extracellular matrix to a number of chondrocytes as claimed. Any difference in process conditions presently claimed from process conditions disclosed by Smith et al will not produce a materially different cartilage construct.

The presently claimed invention is not disclosed in parent application 10/104,677, and the parent application cannot be relied on for a priority date earlier than the filing date the present application.

Response to Arguments

The response argues that Smith et al do not produce a neo-cartilage construct since in the claims this construct is prepared from mature non-dividing metabolically inactive chondrocytes from cartilage that is not vascularized, and the chondrocytes have been treated according to the invention to rejuvenate them. However, Smith et al isolate chondrocytes that are inherently mature (Example 1) since they are adult articular chondrocytes (col 16, line 65). These chondrocytes are inherently non-dividing and inactive. The present specification discloses no source of cartilage for isolating chondrocytes other than disclosed by Smith et al. Articular cartilage

disclosed by Smith et al (col 1, line 43) is hyaline cartilage, and articular chondrocytes isolated by Smith et al (Example 1) produce hyaline cartilage. Applying hydrostatic pressure at a frequency disclosed by Smith et al inherently rejuvenates the isolated chondrocytes as evidenced by Smith et al disclosing (col 11, lines 7-10) that the hydrostatic pressure increases metabolic activity and decreases expression of destructive enzymes of chondrocytes. Articular cartilage is normally not vascularized, and cartilage is not vascularized from which Smith et al isolate chondrocytes.

The response urges that Smith et al does not recognize the concept of neo-cartilage. However, the recognition of an inherent property of a known product does not make the product unobvious and patentable. Due to the similarity of the conditions used by Smith et al to the presently claimed conditions, there is seen no convincing reason why the construct of Smith et al will not be an immature hyaline cartilage (neo-cartilage) construct.

Claim Rejections - 35 USC § 103

Claims 43-48 and 51-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al (6,528,052 B1) in view of Lee et al (6,306,169 B1) and Burg (6,991,652 B2), and if necessary in further view of Atkinson et al (6,511,958 B1).

The invention and Smith et al are described.

Lee et al disclose producing an implant containing cells such as chondrocytes (col 7, line 8) by isolating the cells from tissue, proliferating the cells in a medium containing serum to obtain a

sufficient number of cells, and seeding the cells in a construct (col 7, lines 13-17) such as a collagen sponge (col 12, line 17). A collagen sponge can be infiltrated with an alginate or agarose solution containing the cells, and the alginate or agarose gelled within the sponge (col 13, lines 11-25). This procedure produces a construct having mechanical function that resembles that processed by tissue to be repaired (col 4, lines 28-37).

Burg discloses forming a hydrogel-cell composition for use in forming new tissue such as cartilage. Before the cell are incorporated in a construct, the cells can be expanded in number by culturing in vitro in a medium containing serum (col 7, lines 20-29). Temperature-dependent hydrogels can be used (paragraph bridging cols 5 and 6). The hydrogels have reverse gelation properties, and are liquids at or below room temperature, and gel when warmed to higher temperatures, e.g. body temperature.

When incorporating cells in a scaffold for treatment as disclosed by Smith et al, it would have been obvious to expand the number of cells by *in vitro* culturing in a medium containing serum prior to incorporating the cells in the scaffold as suggested by Lee et al and Burg expanding the number of cells before incorporating the cells in a scaffold for implanting. The resultant construct will be an immature hyaline cartilage construct as presently claimed, and will inherently have a ratio of extracellular matrix to number of chondrocytes of lower than 95:5. Smith et al disclose using a hydrostatic pressure and frequency of applying the pressure that are the same or

substantially the same as used in the present claims. Suspending the chondrocytes of Smith et al in a solution such as a collagen solution before seeding the cells in the matrix is suggested by Lee et al suspending cells in a solution such as collagen solution before seeding (col 6, line 21, and col 13, lines 11-26) that forms a second matrix component. The collagen solution would have been expected to gel and form a scaffold for the chondrocytes. The conditions of dependent claims are suggested by conditions used by the references. Lee et al suggest a sponge and Burg suggests temperature-dependent hydrogels as a matrix for seeding cells to implant. Air contains slightly above 20% oxygen and using slightly less than 20% oxygen as in claim 57 would have been an obvious variation that would not be expected to produce a difference in result. Smith et al disclose 7.5% carbon dioxide (col 17, line 10), and using 5% as in claim 58 is an obvious variation that would not be expected to produce a difference in result. Atkinson et al further disclose repairing cartilage lesions, and if needed would have further suggested conditions that can be used.

Response to Arguments

The response urges that Smith et al do not deal with immature hyaline cartilage, and such cartilage is not suggested by the other references applied. However, as set forth above, the process of Smith et al inherently produces immature hyaline cartilage.

Claim Rejections - 35 USC § 103

Claims 49 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claims 43-48 and 51-60 above, and further in view of Bachrach (7,025,916 B2) (newly applied).

The claims require a Type I collagen solution, which can be a purified pepsin-solubilized bovine collagen dissolved in hydrochloric acid.

Bachrach discloses using pepsin (col 5, line 65) and hydrochloric acid (col 6, line 21) in producing a collagen solution for making collagen fibrils for bioengineering.

When using a collagen gel as the matrix of Smith et al as set forth above, it would have been obvious to produce the gel from a collagen solution produced as suggested by Bachrach.

Claim Rejections - 35 USC § 103

Claims 61 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claims 43-48 and 51-60 above, and further in view of Bellamkonda et al (6,156,572) (newly applied).

The claims require using a perfusion medium containing sodium selenite.

Bellamkonda et al disclose culturing cells in a medium containing sodium selenite (col 13, line 38).

It would have been obvious to incorporate sodium selenite in the culture medium of Smith et al when applying hydrostatic pressure to

obtain the function of sodium selenite as obtained by Bellamkonda et al.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is 571-272-0920. The examiner can normally be reached on Monday-Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

David M. Naff
Primary Examiner
Art Unit 1657

DMN
2/18/07